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Maternal mid-pregnancy lipids and birthweight

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Abstract

Objective—To describe associations among maternal lipids and birthweight and to determine whether pre-pregnancy body mass index (BMI) modifies these associations.

Design—Cohort Study.

Setting—Multiple communities in Michigan, USA.

Population—Participants were a sub-cohort of women from the multi-community Pregnancy Outcomes and Community Health (POUCH) study (1998–2004).

Methods—Maternal total cholesterol, high-density lipoprotein (HDLc), and low-density lipoprotein (LDLc) cholesterol, and triglycerides were assessed at 16–27 weeks' gestation. Women were classified as having normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-pregnancy BMI.

Main Outcome Measures—Sex- and gestational-age-specific BWz-score.

Results—Regression models examined associations among lipids (low: 1st quartile, referent: middle quartiles, high: 4th quartile) and BWz-scores for the total sample and stratified by pre-pregnancy BMI. In adjusted analyses (n=1207), low HDLc was associated with lower BWz-score (β=−0.23, 95%CI: −0.40 to −0.06) while high triglycerides was associated with higher BWz-score (β=0.23, 95%CI: 0.06–0.41). Once stratified by pre-pregnancy BMI, low total cholesterol was associated with lower BWz-score in normal BMI women (β= −0.25, 95%CI: −0.47 to −0.03), while in overweight/obese BMI women, high HDLc was inversely (β= −0.29, 95%CI: −0.54 to −0.04) and high triglycerides was directly associated with BWz-score (β=0.32, 95%CI: 0.07–0.54). Removing women with gestational diabetes/hypertensive disorders did not alter the results.

Conclusions—The associations among maternal lipids and BWz-score vary by lipid measure and pre-pregnancy BMI. Future work should examine whether lipids and pre-pregnancy BMI make unique contributions to the fetal programming of disease.

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Conflicts of Interest

The authors report no conflicts of interest.

Keywords

cholesterol; triglycerides; fetal programming; obesity; fetal growth

Introduction

Maternal lipids during pregnancy are known to increase as part of a normal physiological response to pregnancy, despite hemodilution (1). Increased lipid levels contribute towards hormonal and nutritional support of a healthy pregnancy (2); nevertheless, extremely high levels may induce oxidative stress and have been linked to poorer birth outcomes in animal models (3) and to atherosclerosis in human offspring (4). In contrast, low lipid levels may reflect an inadequate response to pregnancy and have been associated with preterm delivery and lower birthweight (BW) (5).

Previous investigations on associations among maternal lipid profiles and BW have shown that higher triglyceride (TG) levels are related to higher BW and/or increased risk of macrosomia, especially among women with gestational diabetes or a positive diabetic screen (6–11). In addition to TG, increasing low-density-lipoprotein cholesterol (LDLc) levels have been associated with increased odds for macrosomia, while increasing high-density-lipoprotein cholesterol (HDLc) levels decreased these odds (9). On the other end of the BW distribution, intrauterine growth restriction has been associated with lower levels of total cholesterol (TC) and/or LDLc (12, 13).

It has recently been suggested that maternal obesity may influence associations among maternal lipids and fetal development. Misra et. al.(14) showed that HDLc levels measured at multiple times throughout pregnancy were inversely associated with BW, but only among women with overweight/obese pre-pregnancy body mass index (BMI) (i.e. BMI ≥ 25 kg/m^2). They also showed that while BW was directly related to TG measured at early (10–14 weeks) and mid- gestation (22–26 weeks) among normal weight women, TG was only significantly related to BW among overweight/obese women when measured in mid to late pregnancy (22–26 and 32–36 weeks). These results suggest that maternal BMI status may alter maternal metabolic factors during pregnancy leading to changes in fetal development; however, they are based on a fairly small (n=142) and homogeneous sample of women (14).

The aim of this study was to determine whether levels of maternal TC, HDLc, LDLc, or TG measured at mid-pregnancy were associated with sex- and gestational-age-specific BW standard scores (BWz) in a large and diverse sample of women. Secondly, we sought to determine whether maternal pre-pregnancy BMI status modified associations among maternal lipids and BW.

Material and methods

Data from the Pregnancy Outcomes and Community Health (POUCH) Study were used to evaluate the aims. The POUCH study was primarily designed to investigate preterm delivery and has been previously described (15). Briefly, pregnant women were recruited from 52 clinics in five Michigan communities from 1998–2004, and enrolled during their 16^{th}–27^{th}

week of pregnancy (15). Eligibility criteria included singleton pregnancy with no known chromosomal abnormality or birth defect, screening for maternal serum alpha-fetoprotein (MSAFP), maternal age ≥ 15 years, no pre-existing diabetes mellitus, and proficiency in English. All women with high MSAFP levels (i.e. ≥ 2 multiples of the mean) were invited to participate because this biomarker has been previously associated with preterm delivery. Women with normal MSAFP levels were stratified by race/ethnicity and randomly sampled into the cohort. Institutional review boards at Michigan State University, the Michigan Department of Community Health, and nine community hospitals, which collectively covered all study clinics, approved the study.

The POUCH study enrolled 3038 women, and accomplished delivery follow-up for 3019 women. A sub-cohort of women (n=1371) was selected to maximize resources for more detailed study (such as biomarker assays, placental pathology) and to permit sub-analyses of strata of particular interest. The sub-cohort included all women who delivered preterm (<37 weeks), women who delivered at term but had high MSAFP levels, and a race-stratified sample of women with term deliveries and normal MSAFP levels, with oversampling of the African-American stratum. All analyses were weighted according to the probabilities of selection into the cohort and sub-cohort to remove bias due to oversampling from certain strata. Stored blood samples from 62 women in the sub-cohort lacked enough blood for lipid analyses and an additional 102 women lacked data on pre-pregnancy BMI or gestational weight gain, thus the final sample for this study included 1,207 women (88% of the subcohort).

At enrollment, women signed consent forms, completed self-administered surveys and in-person interviews with a study nurse, and had a non-fasting venous blood draw. Prenatal and labor and delivery records were abstracted. Gestational age was calculated using the last menstrual period unless it disagreed by more than two weeks with ultrasound conducted prior to 25 weeks gestation, in which case the ultrasound value was used. Thus, the last menstrual period estimate was used in 76% of the cohort where the two estimates agreed and in 6% of the cohort where only last menstrual period estimates were available. Ultrasound estimates were used in the remaining 18% of the cohort with absent or conflicting last menstrual period estimates. Sex-and gestational-age specific BWz-scores were calculated using means and standard deviations from a reference population (16).

Measurement of blood lipids

Non-fasting blood samples were drawn at a mean gestational age of 22.4 weeks (range: 15–27 wks), centrifuged within 45 minutes of collection, aliquoted (1 ml), and stored at -80°C until analyses. Samples were shipped on dry ice to the Nutrition Lab in the Department of Epidemiology at the University of Pittsburgh for lipid analyses. This laboratory has been included in the Centers for Disease Control and Prevention – National Heart, Lung and Blood Institute (CDC-NHLBI) Lipid Standardization Program since 1982, is Clinical Laboratory Improvement Act (CLIA) certified and participates in College of American Pathologists proficiency programs. TC (mmol/L) was determined using the enzymatic method of Allain et al.(17). HDLc (mmol/L) was measured directly using a homogeneous two-reagent method with materials obtained from Equal Diagnostics. LDLc (mmol/L) was

calculated indirectly using the Friedewald equation: $\mathrm{LDLc}=\mathrm{TC}-\mathrm{HDLc}-0.2*(\mathrm{TG})$, except when total TG exceeded 4.52 mmol/L, in which case LDLc was measured directly using an automated spectrophotmetric assay (LDL Direct Liquid Select) from Equal Diagnostics (18). TG (mmol/L) were determined enzymatically using the Bucolo et. al. procedure (19). Duplicate samples with standards, control sera and serum calibrators were included in each run. The coefficients of variation ranged from 1.3 to 6.7%.

Covariates

The enrollment interview and questionnaire provided information on demographics, medical and reproductive history, pre-pregnancy weight and height (BMI calculated, kg/m^2), and smoking and alcohol intake during pregnancy. For stratified analyses, women were classified as having normal (<25 kg/m^2) or overweight/obese (≥25 kg/m^2) pre-pregnancy BMI. Maternal weight at the time of the blood draw was recorded. Medical record abstraction provided information on gestational weight gain and data for identifying hypertensive disorders and gestational diabetes. Women were classified as having low, recommended or high gestational weight gain based on the pre-pregnancy BMI according to the 2009 Institute of Medicine guidelines (20).

Statistical analyses

Analyses were conducted with SAS version 9.3 (SAS Institute, Cary, NC, USA). Statistical significance was set at a two-sided alpha level of $p<0.05$. Sampling weights were used to remove bias due to oversampling of high MSAFP into the cohort and oversampling of high MSAFP, preterm deliveries, and African Americans into the subcohort. Thus, weighted results account for the POUCH sampling scheme and should reflect the experience of the population of pregnant women that was initially sampled.

Descriptive statistics of participant characteristics were calculated for the total sample and for each stratum of pre-pregnancy BMI. Chi-squared and Student's t-test analyses were used to test for significant differences in participant characteristics by pre-pregnancy BMI. Because lipid values were skewed, log-transformed values (which normalized lipid distributions) were used when calculating mean levels, which were then back-transformed for reporting.

Previous evidence suggests that extreme lipids levels, too low or too high, may mark adverse pregnancy outcomes (21), and therefore our statistical modeling strategy was designed to detect threshold and U-shaped effects. We chose, beforehand, a quartile distribution and categorized women as having low (<25th percentile), referent (25-<75th percentile) or high (≥75th percentile) TC, HDLc, LDLc and TG values. To calculate cut points, we used the normalized log-transformed lipid distributions among women with normal MSAFP values who delivered at term (i.e. healthy pregnancies). Cut points for low and high lipid categorizations, respectively, were <5.12 mmol/L and ≥6.59 mmol/L for TC, <1.50 mmol/L and ≥2.04 mmol/L for HDLc, <2.04 mmol/L and ≥2.53 mmol/L for LDLc, and <1.54 mmol/L and ≥2.45 mmol/L for TG (all values back-transformed from the natural log scale). Unadjusted and adjusted regression models were used to evaluate whether low or high lipid values were associated with mean BWz-score. Since lipid values increase with

gestational week and African Americans are known to have more favorable lipid profiles than Whites, gestational week at the time of blood draw (continuous) and race (White/Others vs. African American) were considered as covariates in all adjusted models (22, 23). Based on previous publications the following covariates were also considered: parity, pre-pregnancy BMI, maternal weight at blood draw, Medicaid insurance status, marital status, education level, age, smoking, and alcohol use during pregnancy. Medicaid insurance status was used a marker of low income as this insurance is only available to pregnant women in the USA who meet eligibility criteria based on federal poverty levels. Any variable that altered estimates of associations between lipid levels and BWz-score by more than 10% was retained in the adjusted models. Gestational weight gain poses a special challenge in these models, as it could be a confounder, mediator, or collider variable. Thus we decided to compare models with and without this covariate and interpret differences cautiously. In a second set of adjusted models, women with gestational diabetes or hypertensive disorders were removed from the analytic sample to determine whether their absence changed parameter estimates for associations among lipids and BWz-score.

Finally, in order to determine whether pre-pregnancy BMI was an effect modifier, formal tests for interaction between pre-pregnancy BMI and each lipid were examined. Significant interaction terms were observed for every lipid except triglycerides, therefore all of the above analyses were repeated within the two strata of normal and overweight/obese pre-pregnancy BMI.

Results

The weighted sample estimates show that our cohort was diverse with 25% African American women and 49% of the women enrolled in Medicaid Insurance (Table 1). Half of all participants were overweight/obese pre-pregnancy. Women with normal pre-pregnancy BMI were significantly more likely to have gestational weight gain within the recommended range, be younger, have more than a high school education, not be enrolled in Medicaid insurance, be White/Other race, be nulliparous, and not be diagnosed with gestational diabetes or hypertensive disorders when compared to women with overweight/obese pre-pregnancy BMI (Table 1). Mean BW was 3340 g (95%CI: 3.31 – 3.38) corresponding to a mean sex- and gestational-age-specific BWz-score of 0.06 (95%CI: −0.01 to − 0.13) (Table 2). Mean lipid values for the total group were similar to those previously reported for second trimester measurements (1). Women with normal pre-pregnancy BMI had significantly lower mean BWz-score and TG values and significantly higher HDLc values compared to women with overweight/obese pre-pregnancy BMI (Table 2).

Within the total sample of women, low HDLc was related to significantly lower BWz-score (β= −0.23, 95% CI: −0.40 to −0.06), while high TG was related to significantly higher BWz-score (β=0.23, 95% CI: 0.06 – 0.41) after adjustment for maternal race, pre-pregnancy BMI, gestational smoking, parity, age and gestational age at time of blood draw (Table 3). Further adjustment for gestational weight gain did not alter associations between lipids and BWz-score, thus we have left this variable out of all adjusted models due to concerns that it may be in the causal pathway. In stratified analyses, low TC (β= −0.25, 95%CI: −0.47 to −0.03) was related to significantly lower BWz-score among women with normal pre-pregnancy

BMI (Table 4). In contrast, among overweight/obese women, high HDLc was related to significantly lower BWz-score (β= −0.29, 95% CI: −0.54 to −0.04) and high TG was related to significantly higher BWz-score (β=0.31, 95% CI: 0.07 – 0.54). Stratified analyses were adjusted for maternal race, gestational smoking, parity, age, and gestational age at blood draw. Removal of women with gestational diabetes (n=61) or hypertensive conditions (n=132) did not significantly alter any results (data not shown).

Discussion

Our results showed that the associations among maternal lipids and mean BWz-score varied by lipid measure and pre-pregnancy BMI. Both HDLc and TG levels were related to BW z-score among overweight/obese women, while BWz-score was related to TC among normal weight women. These findings are not explained by pregnancy complications such as diabetes or hypertension as removal of women with these conditions did not alter results. In the instances where significant associations were found, the beta estimates from adjusted analyses indicated that having low or high lipid levels may impact BW by 0.2–0.4 z-score units. This represents a magnitude of effect of approximately ± 225 g to 300 g for an infant born at term, which could translate into a clinically significant change in BW.

Previous research has shown that lower levels of TC were associated with decreased BW and/or intrauterine growth restriction/small-for-gestational age BW (5, 12, 13). However, results with low HDLc and lower BW are less conclusive with some not considering HDLc (5) and others reporting no significant associations (12). One study among 625 Greek women did find that HDLc levels <50 mg/dl (<1.29 mmol/L) significantly increased odds of small-for-gestational age BW (13). It is important to note that studies on lipids and low BW have involved small samples (n=16 – 100) which may have limited their ability to detect associations among HDLc and BW. On the other end of the BW distribution, similar to our results in the total (non-stratified) sample, several studies have also documented associations between high TG levels and higher BW and/or macrosomia (6–11). Most of these previous studies were in the context of gestational diabetes or impaired glucose tolerance. Thus it is important that we found a similar association among a large sample of predominantly non-diabetic women, and the association was not altered by excluding women with gestational diabetes or hypertensive disorders.

From a biological perspective, it is reasonable to expect that either high or low levels of maternal lipids may affect fetal growth. Triglycerides and free fatty acids directly support fetal growth (2). Throughout pregnancy, placental enzymes hydrolyze LDL and HDL releasing free fatty acids and glycerol which are taken up by trophoblast cells and re-esterified to provide a fat reservoir for the developing fetus (24). There is also evidence that increased maternal lipid levels late in pregnancy allows the woman to spare blood glucose for the fetus, thereby promoting fetal growth (24).

Maternal obesity may impact the maternal metabolic milieu and fetal development (25). It was recently shown that pre-pregnancy BMI altered the trajectory of lipid changes throughout pregnancy (26). Specifically, women with overweight/obese pre-pregnancy BMI had consistently higher TG levels compared to normal weight women, but had a slower rate

of change in TC and LDLc over pregnancy resulting in significantly lower levels of these lipids in the third trimester (26). These results may indicate a dysregulation of the metabolic response to pregnancy among overweight/obese women. In our sample, mid-pregnancy levels of TG were significantly higher and HDLc were significantly lower among women with overweight/obese pre-pregnancy BMI compared to normal weight women, while there were no significant differences in TC and LDLc levels. It is possible that our lipids were measured too early in pregnancy to see differences in TC and LDLc levels caused by the slower rate in change among overweight women.

Misra et al.(14) is the only previous study to consider associations among lipids and BW stratified by pre-pregnancy BMI, as we have done. Their study involved 143 predominantly white, middle class women (72 normal weight and 71 overweight/obese) and measured lipids at five time-points during pregnancy. Their findings showed that among normal weight women, higher BW was related to increasing TG measured at 10–14 weeks or 22–26 weeks gestation. No other lipid measurement was related to BW among normal weight women. In contrast, among overweight/obese women, TG measured at 22–26 or 32–36 weeks was related to higher BW, while increasing HDLc measured anytime after 10 weeks gestational was related to lower BW (14). Our lipids were measured only once at 16–27 weeks of gestation (mean gestational age of blood draw = 22.4 weeks). Our results for women with overweight/obese pre-pregnancy BMI were similar to those of Misra et al for the 22–26 week time-frame (14). However, our results for normal weight women were somewhat different. We saw no significant associations among TG and BWz-score among normal weight women, but instead found that low TC was related to significantly lower BWz-score. The POUCH study included a much larger sample of women with greater diversity, thus it is possible that differences in results reflect greater power to detect associations after controlling for various covariates.

Our finding of effect modification by pre-pregnancy BMI suggests maternal adiposity may alter the metabolic response to pregnancy and/or the fetal growth response to the maternal metabolic milieu. Maternal obesity may also alter placental function and/or substrate delivery leading to differences in observed associations among specific lipids and BWz-score (27). Future studies to elucidate the mechanisms at play are needed as interventions to improve the maternal metabolic profile during pregnancy may be a useful strategy for normalizing BW in the future.

Some limitations should be noted. Similar to most previous studies, we measured lipids only once during pregnancy (5–13), thus we were unable to determine if associations among lipids and BWz-score differed across pregnancy as Misra et al explored (14). We also measured lipids in the non-fasted state, similar to some previous investigations (9, 11). While fasting measures would be preferred, these are often difficult to accomplish during pregnancy. Studies comparing fasting versus non-fasting lipid levels show minimal differences (<5%) for TC, HDLc, and LDLc values, while TG are ~15% higher in the non-fasted state (28, 29). Since we used the Friedewald equation to calculate LDLc based on TG, our LDLc values likely reflect greater variation from fasting values as well. Extra variation induced by using non-fasted lipid levels should affect all women similarly without regard to BW and thus have a non-differential effect, most likely attenuating results. Further, results

from population based studies suggest that non-fasting TG values likely represent remnant lipoproteins and are strongly predictive of adverse events including myocardial infarction and stroke (30). The authors of these reports propose that future clinical care could be simplified by using non-fasting lipid profiles for risk prediction, especially as we spend the majority of our time in the non-fasting state. Our use of internal cut points to define the lowest and highest quartiles of lipids may not be generalizable to other populations; however, we did define the cut points using a low risk obstetric sample (i.e. normal MSAFP, no pre-pregnancy diabetes, term delivery) and healthy ranges for lipids have yet to be established during pregnancy. Results from our study and similar studies on maternal lipid levels and fetal growth in high income countries may not apply to circumstances of low income countries with severe under-nutrition. Finally, in our sample and others, the causal ordering is uncertain as fetal and/or placental irregularities may influence maternal lipid levels and visa versa. Effect modification by maternal pre-pregnancy BMI argues that at least some of the effect begins with the mother.

Despite these limitations, our results add to the existing literature on maternal lipids and BW. The POUCH study provided a relatively large and diverse sample which allowed us to control for important covariates. Thus we were able to expand on the results reported by Misra et al.(14), showing differing associations among lipids and BW based on pre-pregnancy BMI. We were also able to examine TC, HDLc, LDLc, and TG individually in relation to BW, rather than being limited to only one or two of these lipids as some previous reports. Finally, unlike previous investigations that focused on women with gestational diabetes and/or impaired glucose tolerance, we were able to document associations among lipids and BW among a mostly healthy pregnant population, and these associations persisted after removing women with diagnoses of gestational diabetes or hypertensive disorders.

Conclusions

Our results indicate that maternal lipid levels at mid-pregnancy may be related to fetal growth among non-diabetic women, and that maternal obesity may alter associations for lipids and BW. Future studies with multiple prospective measures of lipids are needed to determine the most biologically relevant window for measuring maternal lipids in relation to birth outcomes. It is possible that alterations in lipid metabolism and transfer are part of the biological pathway linking maternal obesity to poor birth outcomes (such as extreme BW valuers) as well as fetal programming of later chronic disease (4, 25, 27). Thus, mechanistic studies are needed to elucidate how maternal obesity may alter maternal lipid production, placental transfer of lipids, and/or fetal response to lipids.

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Abbreviations

BMI	body mass index
BW	birthweight
BWz	birthweight standard score
HDLc	high-density lipoprotein cholesterol
LDLc	low-density lipoprotein cholesterol
MSAFP	maternal serum alpha-fetoprotein
POUCH	Pregnancy Outcomes and Community Health
TC	total cholesterol
TG	triglycerides

References

1. Basaran A. Pregnancy-induced hyperlipoproteinemia: Review of the literature. Reprod Sci. 2009; 16:431–7. [PubMed: 19233944]
2. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002; 19:43–55. [PubMed: 12583601]
3. De Assis SMA, Seguro AC, Helon CMB. Effects of maternal hypercholesterolemia on pregnancy and development of offspring. Pediatr Nephrol. 2003; 18:328–34. [PubMed: 12700957]
4. Napoli C, D'Armiento FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest. 1997; 100:2680–90. [PubMed: 9389731]
5. Edison RJ, Berg K, Remaley A, Kelley R, Rotimi C, Stevenson RE, et al. Adverse birth outcome among mothers with low serum cholesterol. Pediatrics. 2007; 120:723–33. [PubMed: 17908758]
6. Kushtagi P, Arvapally S. Maternal mid-pregnancy serum triglyceride levels and neonatal birth weight. Int J Gynaecol Obstet. 2009; 106:258–9. [PubMed: 19327771]
7. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Ghio A, Giovannitti MG, et al. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med. 2005; 22:21–5. [PubMed: 15606686]
8. Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2010; 89:700–4. [PubMed: 20423280]
9. Clausen T, Burski TK, Oyen N, Godang K, Bollerslev J, Henriksen T. Maternal anthropometric and metabolic factors in the first half of pregnancy and risk of neonatal macrosomia in term pregnancies. A prospective study. Eur J Endocrinol. 2005; 153:887–94. [PubMed: 16322395]
10. Schaefer-Graf UM, Graf K, Kulbacka I, Kjos SL, Dudenhausen J, Vetter K, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care. 2008; 31:1858–63. [PubMed: 18606978]
11. Vrijkotte TG, Algera SJ, Brouwer IA, van Eijsden M, Twickler MB. Maternal triglyceride levels during early pregnancy are associated with birth weight and postnatal growth. J Pediatr. 2011; 159:736–42. [PubMed: 21705016]

12. Ramsay JE, Ferrell WR, Crawford L, Wallace AM, Greer IA, Sattar N. Divergent metabolic and vascular phenotypes in pre-eclampsia and intrauterine growth restriction: Relevance of adiposity. J Hypertens. 2004; 22:2177–83. [PubMed: 15480103]
13. Chatzi L, Plana E, Daraki V, Karakosta P, Alegkakis D, Tsatsanis C, et al. Metabolic syndrome in early pregnancy and risk of preterm birth. Am J Epidemiol. 2009; 170:829–36. [PubMed: 19713286]
14. Misra VK, Trudeau S, Perni U. Maternal serum lipids during pregnancy and infant birth weight: The influence of prepregnancy BMI. Obesity (Silver Spring). 2011; 19:1476–81. [PubMed: 21394096]
15. Holzman C, Bullen B, Fisher R, Paneth N, Reuss L. Pregnancy outcomes and community health: The POUCH study of preterm delivery. Paediatr Perinat Epidemiol. 2001; 15 (Suppl 2):136–58. [PubMed: 11520406]
16. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, et al. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001; 108:E35. [PubMed: 11483845]
17. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem. 1974; 20:470–5. [PubMed: 4818200]
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
19. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem. 1973; 19:476–82. [PubMed: 4703655]
20. Rasmussen KM, Catalano PM, Yaktine AL. New guidelines for weight gain during pregnancy: What obstetrician/gynecologists should know. Curr Opin Obstet Gynecol. 2009; 21:521–6. [PubMed: 19809317]
21. Mudd LM, Holzman CB, Catov JM, Senagore PK, Evans RW. Maternal lipids at mid-pregnancy and the risk of preterm delivery. Acta Obstet Gynecol Scand. 2012; 91:726–35. [PubMed: 22404756]
22. Ford ES, Li C, Pearson WS, Zhao G, Mokdad AH. Trends in hypercholesterolemia, treatment and control among United States adults. Int J Cardiol. 2010; 140:226–35. [PubMed: 19081646]
23. Ford ES, Mokdad AH, Giles WH, Mensah GA. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among us adults: Findings from the National Health And Nutrition Examination Survey, 1999 to 2000. Circulation. 2003; 107:2185–9. [PubMed: 12719276]
24. von Versen-Hoeynck FM, Powers RW. Maternal-fetal metabolism in normal pregnancy and preeclampsia. Front Biosci. 2007; 12:2457–70. [PubMed: 17127255]
25. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. BJOG. 2006; 113:1126–33. [PubMed: 16827826]
26. Vahratian A, Misra VK, Trudeau S, Misra DP. Prepregnancy body mass index and gestational age-dependent changes in lipid levels during pregnancy. Obstet Gynecol. 2010; 116:107–13. [PubMed: 20567175]
27. King JC. Maternal obesity, metabolism, and pregnancy outcomes. Annu Rev Nutr. 2006; 26:271–91. [PubMed: 16704347]
28. Mora S, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation. 2008; 118:993–1001. [PubMed: 18711012]
29. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: Influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008; 118:2047–56. [PubMed: 18955664]
30. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007; 298:299–308. [PubMed: 17635890]

Key Message

Within a large, diverse cohort maternal lipid levels at mid-pregnancy appear to influence fetal growth. Pre-pregnancy body mass index modifies the associations between maternal lipids and birthweight, even when adjusting for covariates or excluding women with gestational diabetes or hypertensive disorders.

Table 1

Participant characteristics presented as n (weighted column percent), Pregnancy Outcomes and Community Health Study, 1998–2004.

	Total Sample N=1207	Pre-pregnancy BMI <25kg/m^2 N=602	Pre-pregnancy BMI ≥25kg/m^2 N=605	Chi-squared p-value
Gestational weight gain				
Low	194 (14.4)	77 (9.7)	117 (19.4)	
Recommended	274 (23.3)	183 (31.0)	91 (15.1)	**<0.001***
High	739 (62.3)	342 (59.3)	397 (65.5)	
Maternal age (years)				
<20	185 (12.9)	118 (17.1)	67 (8.5)	
20-<30	693 (57.5)	317 (52.5)	376 (62.6)	**<0.001***
30+	329 (29.7)	167 (30.4)	162 (28.8)	
Maternal education				
< High School	280 (19.4)	148 (20.3)	132 (18.5)	
High School/GED	334 (26.2)	143 (22.6)	191 (30.0)	**0.047***
> High School	593 (54.4)	311 (57.1)	282 (51.5)	
Relationship Status				
Single	414 (27.3)	199 (24.8)	215 (30.0)	**0.073**
Co-habitation	790 (72.7)	401 (75.2)	389 (70.0)	
Medicaid Enrollment				
Yes	678 (49.0)	315 (43.2)	363 (55.1)	**<0.001***
Maternal Race				
White/Other	717 (75.4)	377 (78.4)	340 (72.3)	**0.011***
African American	490 (24.6)	225 (21.6)	265 (27.7)	
Parity				
Nulliparous	506 (41.8)	295 (49.5)	211 (33.7)	**<0.001***
Gestational Diabetes				
Yes	61 (5.4)	14 (2.3)	47 (8.8)	**<0.001***
Hypertensive Disorders				
None	1077 (90.1)	558 (93.8)	519 (87.0)	
Chronic Hypertension	44 (3.1)	16 (2.0)	28 (4.2)	**0.003***
Preeclampsia/Gestational HT	88 (6.4)	28 (4.2)	58 (8.7)	
Gestational Smoking				
Any	337 (27.6)	164 (25.5)	173 (29.9)	**0.157**
Gestational Alcohol Use				
Any	204 (17.5)	108 (18.1)	96 (16.9)	**0.296**
Timing of Delivery				
Preterm	292 (10.7)	149 (10.8)	143 (10.7)	**0.148**
Term	915 (89.3)	453 (89.2)	462 (89.3)	
Child Gender				

	Total Sample N=1207	Pre-pregnancy BMI <25kg/m^2 N=602	Pre-pregnancy BMI ≥25kg/m^2 N=605	Chi-squared p-value
Male	**615 (49.1)**	**313 (49.2)**	**302 (49.1)**	**0.972**

BMI=Body mass index, GED=General education development examination, HT=hypertension.

*Significant p-value <0.05 comparing pre-pregnancy BMI <25kg/m^2 to pre-pregnancy BMI ≥25kg/m^2.

Table 2

Mean (95% confidence interval) lipid levels and birthweight z-scores for the total sample and stratified by pre-pregnancy BMI, Pregnancy Outcomes and Community Health Study, 1998–2004[a].

	Total Sample N=1207		Pre-pregnancy BMI <25kg/m^2 N=602		Pre-pregnancy BMI ≥25kg/m^2 N=605		Student t-test p-value
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
Total Cholesterol (mmol/L)	5.80	(5.73 – 5.88)	5.84	(5.74 – 5.94)	5.76	(5.65 – 5.88)	0.172
HDL Cholesterol (mmol/L)	1.74	(1.71 –1.77)	1.83	(1.79 – 1.86)	1.65	(1.61 – 1.69)	<0.001*
LDL Cholesterol (mmol/L)	3.01	(2.94 – 3.08)	3.06	(2.97 – 3.15)	2.95	(2.84 – 3.06)	0.072
Triglycerides (mmol/L)	1.96	(1.91 – 2.01)	1.79	(1.73 – 1.84)	2.17	(2.09 – 2.25)	<0.001*
Birthweight z-score	0.06	(−0.01 – 0.13)	−0.06	(−0.16 - 0.04)	0.19	(0.08 – 0.29)	0.003*

BMI, body mass index; CI, confidence interval; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; z, standard score.

[a]Lipid-levels were log-transformed to calculate mean values and confidence intervals, then back-transformed for reporting. Student's t-tests were performed on the log-transformed lipid levels.

*Significant p-value <0.05 comparing pre-pregnancy BMI <25kg/m^2 to pre-pregnancy BMI ≥25kg/m^2

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Table 3

Associations among maternal mid-pregnancy lipid levels and birthweight z-score, Pregnancy Outcomes and Community Health Study, 1998–2004.

	Unadjusted (n=1207)				Adjusted Model[a] (n=1207)			
	R^2	β	95% CI		$adjR^2$	β	95% CI	
TC	0.012				0.139			
<25%		−0.15	−0.33	0.02		−0.15	−0.30	**0.01**
>75%		0.16	−0.01	0.33		0.12	−0.05	**0.28**
HDLc	0.003				0.133			
<25%		−0.12	−0.30	0.05		−0.23*	−0.40	**−0.06**
>75%		−0.09	−0.26	0.08		−0.05	−0.22	**0.11**
LDLc	0.006				0.129			
<25%		−0.10	−0.28	0.09		−0.08	−0.24	**0.09**
>75%		0.13	−0.03	0.30		0.11	−0.05	**0.27**
TG	0.033				0.136			
<25%		−0.20*	−0.36	−0.03		−0.07	−0.23	**0.09**
>75%		**0.32***	**0.14**	**0.50**		**0.23***	**0.06**	**0.41**

β=beta; $adjR^2$ = adjusted R-squared; CI=confidence interval; TC=total cholesterol, HDLc, high density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol; TG, triglycerides.

[a]The adjusted model includes maternal race (white/other vs black), pre-pregnancy BMI (cont.) gestational smoking (yes/no), parity (nulliparous/parous), maternal age (<20, 20–30, 30+), and gestational age at blood draw (cont.).

*significant p-value<0.05.

Table 4

Associations among maternal mid-pregnancy lipid levels and birthweight z-score stratified by pre-pregnancy BMI, Pregnancy Outcomes and Community Health Study, 1998–2004.

Pre-pregnancy BMI <25 kg/m^2								
	Unadjusted (n=602)				**Adjusted Model[a] (n=602)**			
	R^2	**β**	**95% CI**		**adjR^2**	**β**	**95% CI**	
TC	0.035				0.137			
<25%		−0.32*	−0.56	−0.09		−0.25*	−0.47	**−0.03**
>75%		0.21	−0.02	0.44		0.18	−0.06	**0.42**
HDLc	0.011				0.115			
<25%		−0.24	−0.50	0.02		−0.25	−0.50	**0.01**
>75%		0.07	−0.15	0.29		0.06	−0.16	**0.28**
LDLc	0.027				0.121			
<25%		−0.25*	−0.48	−0.01		−0.17	−0.39	**0.06**
>75%		0.23*	0.00	0.46		0.22	−0.01	**0.45**
TG	0.015				0.109			
<25%		−0.21*	−0.43	−0.00		−0.11	−0.32	**0.10**
>75%		0.13	−0.14	0.40		0.11	−0.16	**0.38**

Pre-pregnancy BMI ≥25 kg/m^2								
	Unadjusted (n=605)				**Adjusted Model[a] (n=605)**			
	R^2	**β**	**95% CI**		**adjR^2**	**β**	**95% CI**	
TC	0.002				0.117			
<25%		0.002	−0.26	0.26		−0.03	−0.26	**0.21**
>75%		0.10	−0.15	0.34		0.02	−0.21	**0.25**
HDLc	0.011				0.131			
<25%		−0.14	−0.37	0.10		−0.22	−0.44	**0.07**
>75%		−0.29*	−0.57	−0.01		−0.29*	−0.54	**−0.04**
LDLc	0.000				0.117			
<25%		0.01	−0.25	0.28		−0.01	−0.25	**0.23**
>75%		0.02	−0.22	0.26		−0.02	−0.24	**0.20**

Pre-pregnancy BMI ≥25 kg/m^2								
	Unadjusted (n=605)				Adjusted Model[a] (n=605)			
	R^2	β	95% CI		adjR^2	β	95% CI	
TG	0.041				0.136			
<25%		−0.15	−0.39	0.09		−0.04	−0.26	**0.19**
>75%		**0.39**[*]	**0.14**	**0.62**		**0.31**[*]	**0.07**	**0.54**

BMI=Body mass index; β=beta; adjR^2 = adjusted R-squared; CI=confidence interval; TC=total cholesterol; HDLc=high density lipoprotein cholesterol; LDLc=low density lipoprotein cholesterol; TG=triglycerides.

[*] significant p-value<0.05

[a] The adjusted model includes maternal race (white/other vs black), gestational smoking (yes/no), parity (nulliparous/parous), maternal age (<20, 20–30, 30+), gestational age at blood draw (cont.)